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PATENT  
Docket No.: 026549-000100US  
Client Ref. No.: 30836

On \_\_\_\_\_

TOWNSEND and TOWNSEND and CREW LLP

By: \_\_\_\_\_

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Ronit Eisenberg

Patent No.:

Issued:

Application No.: 10/009,809

Filed: April 26, 2002

For: CELL PENETRATING ANTI-ALLERGIC PEPTIDES

Confirmation No.: 1519

Examiner: Crowder, Chun

Art Unit: 1644

RULE 132 DECLARATION

Commissioner  
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for  
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Sir:

I, Dr. Ehud Razin, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. **The Exhibits (1 and \_ attached hereto are incorporated herein by reference.**

2. I received a Ph.D. in Immunology/Cell Biology from the Weizmann Institute of Science in 1980.

A copy of my curriculum vitae is attached as Exhibit 1.

3. I am presently employed at the Hebrew University of Jerusalem and am primarily responsible for teaching and research.

4. I have read and am familiar with the contents of the application. I understand that the Examiner has a single rejection based on obviousness that is based on a combination of three references. The references are Holgate as a primary reference in view of Aridor and Lin. Holgate is cited as disclosing that agents that inhibit mast cell degranulation are recognized for treatment of diseases such as asthma. Aridor discloses KNNLKECGLY which is a mast cell activation inhibitor designated Gai3 C-terminal peptide. Lin discloses the preferred cell penetrating peptide from Kaposi fibroblast growth factor [KFGF].

5. This invention is the surprising discovery that of four different cell penetrating peptides (CCP) only one CCP was able to successfully deliver two mast cell activation inhibitors in a biologically active manner. Because the prior art literature would suggest to those of skill that CCPs are interchangeable, it is surprising that the choice of CCP would be critical for obtaining biological activity. Accordingly, we have to conclude that the field of using cell penetrating peptides to deliver biologically active proteins is far less predictable than the Examiner believes it to be and that the applicants' results as embodied in the pending claims are both surprising and advantageous..

The following statements provide objective, scientific reasons for the above conclusion.

6. It is my understanding that the rejection of the pending claims is based on the proposition that Lin's teaching of the CCP, (AAVALLPAVLLALLAP) as a tool for delivery of biologically active cargo peptides renders the claimed combinations of AAVALLPAVLLALLAP in reading frame fusions with  $G\alpha i_3$  or  $G\alpha t$  C-terminal peptides obvious and unpatentable. In brief, the Examiner believes that upon reading the three references, one of skill would be motivated by Holgate to combine the KFGF CCP of Lin with the mast cell activation inhibitor of Aridor,  $G\alpha i_3$ , with a reasonable expectation that the combination would inhibit mast cell activation.

It is also my understanding that evidence of unpredictability or surprising results can legally refute this conclusion and lead to the rejection being withdrawn.

It is my further opinion that both unpredictability and surprising results have been demonstrated by the applicants' work and by the literature already of record.

7. More specifically, we know that of the four CCPs tested only one CCP was able to deliver the two mast cell activation inhibitors,  $G\alpha i_3$  or  $G\alpha t$ , as a biologically active inhibitors. The table below summarizes Applicants' results as described in the specification and in the Jones et al. publication.

CHIMERIC PEPTIDE			RESULTS
Hu Int	$G\alpha i_3$	SEQ ID NO: 6	No inhibition of histamine secretion
KFGF	$G\alpha i_3$	SEQ ID NO: 7	Inhibited histamine secretion
Dros	$G\alpha i_3$	SEQ ID NO: 10	Induced histamine

			secretion
Hu Int	Gat	SEQ ID NO: 11	No inhibition of histamine secretion
KFGF SEQ ID NO: 3	Gat	SEQ ID NO: 12	<b>Inhibited histamine secretion</b>
Dros	Gat	SEQ ID NO: 13	Induced histamine secretion
TP-10	Gai <sub>3</sub>	Jones <i>et al.</i>	No inhibition of beta-hexoseaminidase secretion

8. From this data, it is clear that only Lin's CCP, KFGF is able to both deliver mast cell activation inhibitors and maintain their biological activity as inhibitors of mast cell activation . The Examiner says that this is predictable from the literature. I respectfully disagree.

Lin discloses that KFGF sequence transported two biologically active cargo peptides and generally states that KFGF can be used to transport other peptides. But similar reports exist for each of the other CCPs tested by applicants. The Hawiger review article discloses that the CCP designated integrin  $\beta_3$  is just as able as KFGF to transport functional peptides into a cell (see page 189, 2nd column). Finally Derossi *et al.* describes the *Drosophila* CCP as successfully delivering biologically active compounds inside live cells (page 18188, 2nd col).

From page 7 of the Office Action, the Examiner appears to interpret this literature as leading one of skill to believe that there is a reasonable expectation that any

combination of CCP with any biologically active peptide will lead to the observation of biological activity in a cell.

I respectfully disagree. There are several scientific and objective reasons why fusing a CCP to a biologically active peptide might not result in observation of expected biological activity. These reasons include improper folding of the fusion peptide resulting in conformational changes that render the cargo peptide inactive; the degradation of the foreign peptide; sequestering of the peptide in endosomes or the ability of the CCP sequence to trigger a biological response, such as mast cell degranulation (e.g. positively charged CCP might function as basic secretagogues of mast cells).

Indeed, this appears to be the case for fusion of CCP with either  $G\alpha i_3$  or  $G\alpha t$ . The data from applicants' laboratory and from the Jones *et al.* group demonstrate that not any CCP can maintain the biological activity of  $G\alpha i_3$  or  $G\alpha t$ . Of four CCPs, only KFGF was the only CCP able to both internalize and maintain the inhibitory activity of both  $G\alpha i_3$  and  $G\alpha t$ . Thus the combination provides a surprisingly advantageous result that was not predictable from the prior art.

I do note the Examiner's statement on page 7 that the table on page 9 with reference to the prior literature describing the various CCPs fail to demonstrate that Lin's CCP is unpredictable as a delivery tool. While this is true, there was no academic reason *a priori* to believe that any of the other CCPs would fail to deliver  $G\alpha i_3$  and  $G\alpha t$  while maintaining its expected biological activity. But the evidence established by the record indicates that this is not true. There is obviously something special about the two mast cell activation inhibitors or with Lin's CCP that makes the claimed combination functional compared to the other three CCPs.

For these reasons, I conclude without hesitation that the claimed combinations of AAVALLPAVLLALLAP with either G $\alpha$ i<sub>3</sub> or G $\alpha$ t to yield a functional inhibitory effect on mast cell activation in light of failure with three other CCPs of equal status was unpredictable, surprising and of great value.

This Declarant has nothing further to say.

Dated: May 6 2007

Dr. Ehud Razin Ehud Razin

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## CURRICULUM VITAE

Name: Ehud Razin  
Birthdate: July 14, 1947  
Marital Status: Married (Michal), two children: Ayelet (1979),  
Jonatan (1986).  
Title: Professor of Biochemistry, Hebrew-University,  
Hadassah Medical School.  
Dr. Marcus Rabwin Chair in Cancer Research

Research Interests: Biology of Mast Cells

### EDUCATION:

1965 - 1968 Captain, Israeli Army  
1970 - 1973 B. Sc. Biology - Hebrew University of Jerusalem  
1973 - 1975 M. Sc. Microbiology - Hebrew University of  
Jerusalem  
1976 - 1980 Ph.D. Immunology - Weizmann Institute of Science

### PROFESSIONAL EXPERIENCE:

2005- Dean Faculty of Medicine Hebrew University  
2001-2005 Chairman of the Faculty's Planning &  
Development Committee  
1998-2001 Chairman Biochemistry Department  
1996- Professor of Biochemistry  
1997-8 Visiting Scientist of NIAMS, NIH  
1993 July-December Visiting Scientist, NIH, U.S.A.  
  
1991-1996 Assoc. Professor in Biochemistry, Hebrew University  
of Jerusalem  
1987 - 1991 Senior Lecturer in Biochemistry, Hebrew University of  
Jerusalem.  
1983 - 1987 Lecturer in Biochemistry, Hebrew University of  
Jerusalem.  
1982 - 1984 Research Fellow - Immunopharmacology, Harvard  
Medical School, Boston, MA, USA.  
1980 - 1981 Research Fellow - Immunology, Memorial Sloan-  
Kettering Cancer Centre, NY, USA.  
1989 - 1990 Visiting Professor, Biomedical Research Centre, UBC,  
Vancouver, Canada.  
1987 - 1989 Consultant, Syntex Research Co., Palo Alto, CA, USA

### AWARDS:

1979 DAAD Scholarship  
1980 Chaim Weizmann Fellowship

### SOCIETIES:

1983 American Association of Immunologists

1994                    CoLLEGIUM INTERNATIoNALE  
ALLERGoLoGICUM (CIA).  
1998                    American Society for Biochemistry and Molecular  
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## **Ehud Razin:**

### **Publications**

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  6. Razin, E., Rifkind, A.B., Cordon-Cardo, C., Good, R.A. Selective growth of a population of human basophil cells in vitro. *Proc Natl Acad Sci U S A* 1981; 78: 5793-6.
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  14. Mencia-Huerta, J.M., Lewis, R.A., Razin, E., Austen, K.F. Antigen-initiated release of platelet-activating factor (PAF-acether) from mouse bone marrow-derived mast cells sensitized with monoclonal IgE. *J Immunol* 1983; 131: 2958-64.
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71. \* Lee, Y.N., Nechushtan, H., Figov, N., Razin, E. The function of lysyl-tRNA synthetase and Ap<sub>4</sub>A as signaling regulators of MITF activity in Fc $\epsilon$ RI-activated mast cells. *Immunity* 2004; 20: 145-51.
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\* Faculty of 1000

\*\* Faculty of 1000 top 10 percent.